Environmental and Molecular Mutagenesis 39:82–88 (2002)

Meeting Reports

Recent Trends in Breast Cancer Incidence and Mortality

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Breast cancer accounts for one-third of cancer diagnoses and 15% of cancer deaths in U.S. women. Its 192,000 cases and 40,000 deaths in 2001 make it the most common incident cancer (excluding superficial skin cancers) and second leading cause of cancer death. Over one-half of the 300,000 breast cancer deaths worldwide in 1990 (the latest year with such data) occurred in developed countries, but annual mortality rates ranged from 27/100,000 women in northern Europe to 4/100,000 women in Asia. Incidence data are less complete, although 1988–1992 rates varied threefold: low in Asia, intermediate in South America and Eastern Europe, and high in North America and Western Europe. Migrant studies suggest that lifestyle factors largely explain these international differences. U.S. incidence rates are generally 20%–40% higher in white women than in non-white women, but are higher in young (under age 40) black women than in young white women. Incidence rates rose in the 1970s, leveled off in the 1990s, and are declining for young women. Women in some areas of the northeast U.S. have twofold higher mortality than that of other U.S. women, but reproductive and socioeconomic characteristics explain much of that difference. In the 1970s and 1980s, mortality rates held steady in developed countries but rose in developing countries. Since 1987 mortality rates fell by 25% as a result of earlier detection and improved treatment. Age–period–cohort analyses indicate that changes in recognized risk factors may affect mortality patterns. Continued analysis of international and intranational trends may reveal targets for multidisciplinary intervention and prevention efforts. Environ. Mol. Mutagen. 39:82–88, 2002. Published 2002 Wiley-Liss, Inc.†

Key words: epidemiology; age–period–cohort analyses; incidence rates; mortality rates; breast neoplasms

IMPACT IN THE UNITED STATES

Breast cancer, the second most frequent cause of cancer death among American women, accounts for 15% of all cancer deaths among women; only lung cancer causes more cancer deaths [Greenlee et al., 2000]. Based on data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program [Ries et al., 2000], 30% of all incident cancers among women are breast cancer, which makes it the most frequently diagnosed cancer [Greenlee et al., 2000]. The American Cancer Society estimated that 192,000 cases and 40,000 deaths would occur among U.S. women during 2001. Breast cancer is rare among men, with only 1400 cases and 400 deaths estimated for the year 2000 in the United States.

AGE AND LIFETIME RISK OF DEVELOPING BREAST CANCER

The risk of breast cancer increases rapidly with age during childbearing years (Fig. 1). After menopause, rates continue to increase, but at a less rapid pace. Based on data from 1995 to 1997, the lifetime risk among U.S. women of being diagnosed with breast cancer is 12.8%, or 1 in 8 women, and the lifetime risk of dying from breast cancer is 3.3%, or 1 in 30 women [Ries et al., 2000]. The "1 in 8" statistic represents a cumulative lifetime risk of breast cancer diagnosis for a woman who lives past age 85. On average, in a cohort of 1000 women followed from birth to death, 128 women will develop breast cancer. At younger ages, short-term risk is, in fact, lower than 1 in 8: a woman in her 30s has a 1 in 250 probability of developing breast cancer before age 40, whereas a woman in her 60s has a 1 in 36 probability of developing breast cancer before age 70 [Phillips et al., 1999]. In addition, the longer a woman lives

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Received 25 September 2001; provisionally accepted 1 November 2001; and in final form 29 November 2001

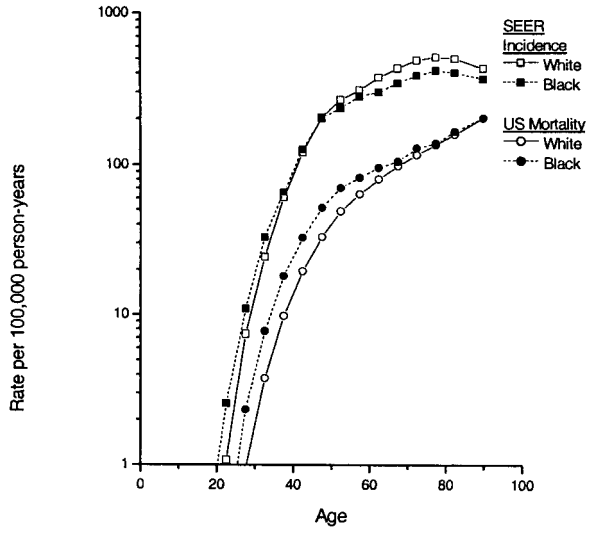

Fig. 1. Age-specific SEER incidence and U.S. mortality rates: female breast cancer (1990–1997).

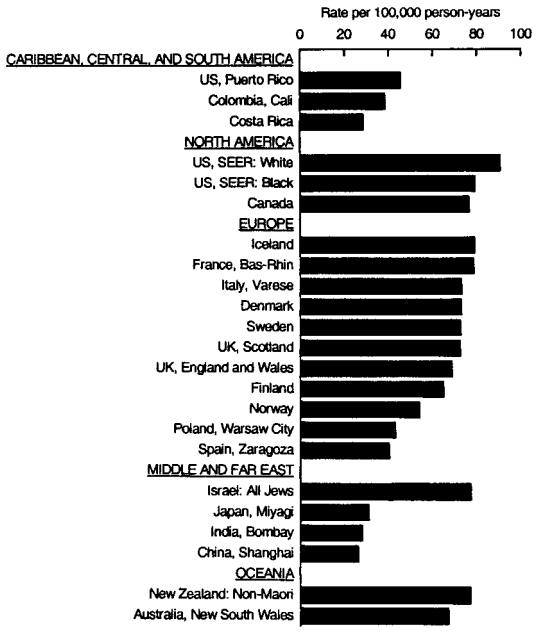

Fig. 2. International variation in female breast cancer incidence: cancer in five continents (1988–1992).

without breast cancer, the lower her subsequent risk of developing breast cancer [Armstrong et al., 2000]. Regardless of how risk is expressed, breast cancer is an important cause of premature morbidity and mortality.

INTERNATIONAL GEOGRAPHIC VARIATION

As the leading cause of cancer death among all women worldwide, breast cancer accounted for more than 300,000 deaths in 1990: 174,100 deaths occurred in developed countries and 139,500 occurred in developing countries [Pisani et al., 1999]. Estimated 1990 mortality rates (per 100,000 woman-years, age-adjusted to the world standard) varied more than sixfold internationally, from less than 4.3 in China to 26.7 in northern Europe. (Unless otherwise noted, "rate" hereafter refers to number of events per 100,000 woman-years.) Rates were also low (less than 15) in Japan, other parts of Asia, Africa, and central America; intermediate (around 20) in South America and southern Europe; and highest (more than 23) in western Europe and North America. From the mid-1970s to the mid-1980s, the international differences in rates narrowed as mortality rates remained relatively stable in many of the countries with high rates but increased in many of the countries with low rates [Aoki et al., 1992].

Mortality data generally exist at the national level because death certificates are considered legal documents, although incidence data from population-based cancer registries are not as widely available. Data from several dozen well-run registries around the world for 1988 to 1992 suggest that incidence rates (age-adjusted to the world standard) varied more than threefold internationally. Annual rates were lowest (less than 32) in parts of China, Japan, India, and Costa Rica; intermediate (between 40 and 60) in South America, the Caribbean, and Eastern Europe; and highest (above 70) in western Europe, Canada, and North America (Fig. 2) [Parkin et al., 1997]. Geographic variation also appeared within many countries, but intranational differences were considerably smaller than international differences. Rates in urban areas generally exceeded those in neighboring rural areas [Muir et al., 1987].

MIGRANT STUDIES

Some portion of these international rate variations is undoubtedly spurious—incomplete reporting, inconsistent diagnostic patterns, and different treatment modalitites across countries account for some of the rate variation—but the consistent pattern of higher rates in certain regions suggests true differences in underlying breast cancer risk across nations. Migrant studies, which explore whether genetic factors or lifestyle and environmental factors might explain rate differences, suggest that lifestyle and environment dramatically, and rather quickly, affect breast cancer risk. The annual incidence rate among Chinese women living in Shanghai was two-thirds the rate among Chinese women living in Hong Kong and Singapore and less than one-half the rate among Chinese women living in Hawaii and San Francisco (Table I) [Parkin et al., 1997]. Similarly, rates for Japanese women in Hawaii, San Francisco, and Los Angeles were twice those for Japanese in Japan. Within Israel, women born in Africa or Asia were at reduced risk compared to those born in Israel, Europe, or America.

Breast cancer risk among migrants approaches risk among native-born populations [Stanford et al., 1995] and is

TABLE 1. Variation in Breast Cancer Incidence Rates Among Women, 1988–1992[a]

Group and place	Cases	Rate[b]
Chinese		
China, Shanghai	6084	26.5
Hong Kong	5392	34.0
US, Los Angeles: Chinese	266	36.8
Singapore: Chinese	2187	39.5
US, San Francisco: Chinese	459	55.2
US, Hawaii: Chinese	159	57.6
Japanese		
Japan, Osaka	7544	24.3
Japan, Miyagi	2440	31.1
US, Los Angeles: Japanese	319	63.0
US, San Francisco: Japanese	138	68.4
US, Hawaii: Japanese	903	72.9
Israeli		
Israel: Jews born in Africa or Asia	1963	56.5
Israel: Jews born in America or Europe	4838	87.9
Israel: Jews born in Israel	1802	90.5

[a]Source: Parkin et al., 1997.
[b]Per 100,000 woman-years, age-adjusted using the world standard.

affected by both the age at and time since migration. Asian Americans born in Asia were at lower risk than Asian Americans who always lived in the United States. Among Asian Americans who migrated to the United States, migration at older ages was associated with a lower risk than migration at younger ages. In addition, recent migrants had a lower risk than migrants who had lived in the United States for more than 20 years. In subsequent generations, risk continued to increase and approach the risk among native-born populations [Ziegler et al., 1993]. Age itself is a major risk factor for all epithelial carcinomas, including breast cancer, but age is also closely related to key reproductive events that are specifically associated with risk (i.e., age at menarche, age at first birth, or age at menopause) [Kelsey et al., 1993]. Whether migration occurs before or after these key events might be especially critical for subsequent risk in migrants, and future studies should attempt to explore risk associated with time since (or before) these reproductive and menstrual events in migrants.

RACIAL AND ETHNIC GROUPS WITHIN THE UNITED STATES

Within the United States during 1988 to 1992, breast cancer incidence rates (age-adjusted to the world standard) were highest among non-Hispanic white women (Table II) [Parkin et al., 1997]. Rates among African American women were 10%−20% lower. Rates among Asians and Hispanics were one-half to two-thirds those of whites; American Indian women were at notably low risk.

The racial and ethnic differences between U.S. white women and African Americans reveal an interesting age phenomenon (Fig. 1). Age-specific incidence rates for Af-

TABLE II. Variation by Racial and Ethnic Group Within the United States in Breast Cancer Incidence Rates Among Women, 1988–1992[a]

	Los Angeles		San Francisco		Hawaii		Connecticut		Seattle		Detroit		Atlanta		New Mexico		Iowa		Utah	
Group	Cases	Rate[b]	Cases	Rate[b]	Cases	Rate[b]	Cases	Rate[b]	Cases	Rate[b]	Cases	Rate[b]	Cases	Rate[b]	Cases	Rate[b]	Cases	Rate[b]	Cases	Rate[b]
Non-Hispanic white[c]	15,823	103.7	9080	103.3	856	96.5	11,135	93.3	10,380	92.5	10,265	91.9	4253	89.9	2625	86.3	9716	85.3	3394	75.8
Black	2389	80.9	1056	83.7	—[d]	—	604	84.5	—	—	2328	80.8	1158	72.3	—	—	—	—	—	—
Filipino	480	69.3	333	65.3	259	57.4	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Japanese	319	63.0	138	68.4	903	72.9	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Hispanic white	3186	57.4	815	70.8	—	—	—	—	—	—	—	—	—	—	856	61.3	—	—	—	—
Chinese	266	36.8	459	55.2	159	57.6	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Korean	97	21.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Hawaiian	—	—	—	—	360	83.9	—	—	—	—	—	—	—	—	—	—	—	—	—	—
American Indian	—	—	—	—	—	—	—	—	—	—	—	—	—	—	80	28.3	—	—	—	—

[a]Source: Parkin et al., 1997.
[b]Per 100,000 woman-years, age-adjusted using the world standard.
[c]All whites in Hawaii, Connecticut, Detroit, and Atlanta; all women in Seattle, Iowa, and Utah.
[d]—, Data not available.

rican American women exceed rates for white women under age 40, but age-specific rates past age 40 are higher for white women than for African Americans. Among women over 40, most of this difference is apparently attributable to differences in well-recognized reproductive and menstrual risk factors: later ages at first birth, lower parity, and earlier ages at menarche, which increase risk, are more common among U.S. white women. For younger women, however, established risk factors do not appear to explain the higher rates among African Americans [Brinton et al., 1997], and future studies should explore hypothesized risk factors, such as in utero or environmental exposures. Mortality rates for all ages show an excess among African Americans than among whites.

GEOGRAPHIC VARIATION AMONG WHITES IN THE UNITED STATES

Breast cancer mortality rates vary considerably by geographic region within the United States, with notably high rates in parts of the Northeast and lower rates across the South [Devesa et al., 1999]. The age-adjusted (to 1970 U.S. standard) rates among white women varied more than twofold, ranging from 16 to 33; they were higher than 30 in urban areas of the Northeast and Midwest and 20 or lower across the South and Rocky Mountain states. The regional excess of breast cancer across the Northeast, especially in urban centers, has persisted for over four decades [Mason et al., 1975; Pickle et al., 1987; Kulldorff et al., 1997] and likely reflects a combination of reproductive characteristics and sociodemographic factors [Pickle et al., 1987]. The pattern is most pronounced among postmenopausal women; there is little geographic variation among premenopausal women [Blot et al., 1977]. However, the North–South differences have diminished over time because mortality rates have risen in many areas of the South, including rural areas of Appalachia [Pickle et al., 1987]. Two recent studies showed that adjustment for differences in reproductive (ages at first birth and ages at menopause) and other (body mass index and alcohol use) variables explained a large part of the observed geographic variation in breast cancer mortality [Sturgeon et al., 1995; Laden et al., 1997]. Average 1972–1991 mortality rates for white women in the Northeast were significantly higher than rates for white women in the Midwest, South, or West; rates for African Americans suggested a north–south gradient [Tarone et al., 1997]. Nonetheless, there continues to be interest in assessing the potential association between dietary or environmental risk factors and regional breast cancer rates.

TEMPORAL TRENDS IN INCIDENCE RATES

U.S. incidence rates (age-adjusted to 1970 U.S. standard) during the past 2.5 decades have generally increased for both African Americans and whites; rates were consistently

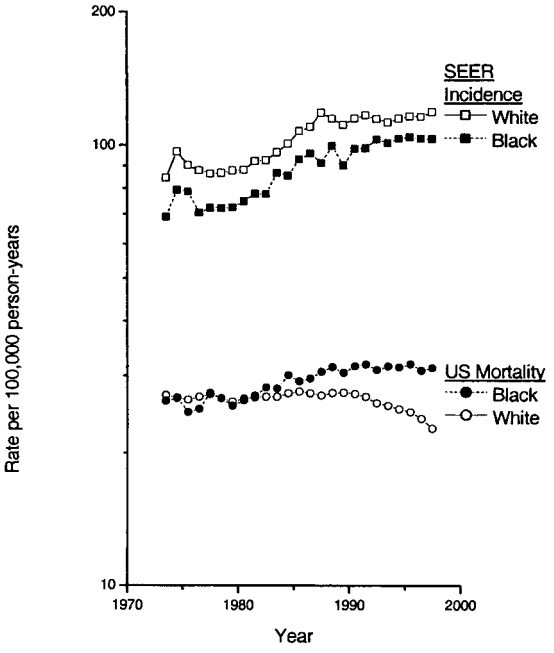

Fig. 3. Age-adjusted (1970 U.S.) SEER incidence and U.S. mortality rates: female breast cancer by single year (1973–1997).

10%−20% higher among whites (Fig. 3). Increases during the early 1970s were most likely related to heightened awareness and detection in response to the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. Steeper increases during the 1980s may have been related to the increasing use of mammography [Miller et al., 1993]. The recent but expected leveling off of U.S. incidence rates further suggests that a lead-time bias attributed to mammography-detected cancers contributed to the increases during the 1980s [Wun et al., 1995]. Rising incidence has been more pronounced for estrogen receptor–positive tumors, particularly among older women [Glass et al., 1990].

The increases in invasive breast cancer incidence were largely attributed to the diagnosis of localized cases (i.e., lower clinical stage), with rates increasing more than 75% among both white and African American women from 1975–1977 to 1995–1997 in the U.S. Rates for regional and distant disease did not change greatly. Rates for in situ carcinoma, which is less frequently diagnosed than invasive carcinoma, also rose rapidly during that period. Increases in localized disease occurred among white women of all ages but were most pronounced among women 60 to 79 years of age. When the size of the tumor was considered, the diagnosis of cancers smaller than 2 cm rose much more rapidly than diagnosis of larger tumors [Miller et al., 1993]. This "stage shift" toward increasing detection and diagnosis of earlier lesions is expected with widening use of mammographic screening.

Incidence rates increased for most countries worldwide since at least the 1970s. The overall percentage increase

varied dramatically, from roughly 20% increases in Europe to approximately 60% in Eastern Europe and Asia, and even 120% in Japan [Ursin et al., 1994]. Interpretation of these increases is not straightforward, however, because the particular contributions of increased detection by mammographic screening (especially in high-risk countries) and improved quality of data collection and classification (especially in developing countries) are difficult to differentiate [Ursin et al., 1994]. Incidence trends can be difficult to compare over time or across groups because of the extent to which inconsistent diagnosis patterns or reporting can affect rates. Nevertheless, the consistent pattern of increasing incidence in many countries suggests a true increase in breast cancer risk during the last 30 years.

TEMPORAL TRENDS IN MORTALITY RATES

During the four decades from 1950 to 1989, age-adjusted (to 1970 U.S. standard) breast cancer mortality rates among white women in the U.S. remained relatively constant, whereas rates among non-white women increased steadily [Devesa, 2000]. Mortality rates among white and African American women were similar in the 1970s, but since the early 1980s breast cancer mortality rates among whites have declined, whereas rates among African Americans continued to increase slightly [Ries et al., 2000] (Fig. 3). After 1989, mortality rates among white women dropped dramatically and fell below rates among non-white women; a combination of better early detection, increasing use of screening mammography, and the introduction of adjuvant therapy contributed to this decline [Chu et al., 1996]. Age-adjusted (to 1970 U.S. standard) rates in 1997 were 31 and 23 among African Americans and whites, respectively. In 2000, the 25% decline in mortality rates for U.S. and U.K. women ages 20–69 reinforces the beneficial effects of recent screening efforts and treatment advances [Peto et al., 2000].

Age-specific mortality rate changes over time also showed some racial and ethnic differences [Chu et al., 1999]. Between 1980 and 1995, mortality rates for both U.S. white and African American women under age 40 decreased, whereas rates for women over 40 diverged. Around 1990, rates among U.S. white women ages 40–79 decreased and rates among African American women ages 40–69 leveled off but did not decrease.

Outside the U.S., mortality rates since 1970 increased in some countries [Coleman et al., 1993]. Although rates in England and Norway did not increase, rates in other European countries, such as Spain and Yugoslavia, and Asian countries, such as Singapore and Japan, increased by 30%−50%. Between 1989 and 1993, age-adjusted (to the world standard) mortality rates fell by 9% in the U.S. (for white women), 9% in England, and 10% in Canada. Better detection and treatment contributed to those declines, but in different relative proportions. In the U.S. earlier use of widespread mammographic screening, which led to increased detection of localized (i.e., treatable) lesions, combined with the later introduction of tamoxifen therapy, led to the dramatic mortality declines. England and Canada adopted mass screening at later dates, but used tamoxifen therapy earlier and more extensively [Chu et al., 1996].

Previously noted incidence increases since the 1970s would be expected to generate subsequent increases in mortality rates. However, lead-time bias, concurrent changes in clinical treatment, and the 20-year median survival time among women newly diagnosed with breast cancer indicate that incidence and mortality trends will not necessarily act in concert [Ries et al., 2000].

AGE–PERIOD–COHORT ANALYSES OF MORTALITY TRENDS

Age–period–cohort analyses simultaneously assess risk across age, calendar period, and birth cohorts [Robertson and Boyle, 1998], and have been used extensively to understand potential reasons for the observed changes in breast cancer mortality rates. Changes in birth-cohort trends can indicate changes in the presence or level of etiologic factors at the population level (e.g., a new risk factor or protective factor). Changes in calendar-period trends can indicate new advances in or increasing use of detection or treatment methods [Chu et al., 1999]. Mortality data from Taiwan, where age-adjusted incidence and mortality rates doubled between the 1970s and late 1980s, revealed the effects of both changing risk factors and increased detection and diagnosis. Birth-cohort trends show that women born after the 1930s are at higher risk than women born before 1930. These women born after the 1930s, who were in their reproductive years during nationwide birth-control programs and other sociodemographic changes in the 1960s, in general had fewer children and had children at later ages than did women born before 1930. Calendar-period trends indicate that risk has been increasing steadily since 1964, when diagnostic efforts increased. Together, a pattern of truly increasing risk, apparently attributable to changes in lifestyle and better detection, accounts for the observed rate changes [Che et al., 1995].

Age–period–cohort analyses shed light on mortality rate differences within countries. Mortality rates between 1973 and 1995 were identical for U.S. white and African American birth cohorts [Chu et al., 1999]. Combined with similarly decreased mortality rates among both white and African American women under age 40, these data suggest that different distributions of recognized risk factors are unlikely to explain the higher mortality rates among young African Americans. Calendar-period trends also decreased for both groups after 1980, but fell more dramatically for white women. In theory, advances in medical interventions should benefit all population groups equally, and therefore the calendar-period data suggest that African Americans bene-

fited less from recent medical advances. Whether lower effectiveness or decreased access among African Americans was responsible is unclear.

Birth-cohort trends reflect demographic patterns that are related to population changes in recognized breast cancer risk factors. The lower risk for U.S. and Canadian women born between 1924 and 1938 (compared to women born before 1924) has been attributed to the higher fertility rates after World War II—for these women were the mothers of the "baby boomers" (women born immediately after World War II)—and to possible dietary restriction at early ages during the Great Depression [Blot et al., 1987; Tarone et al., 1997]. Lower fertility, delayed childbearing, and opportunity for oral contraceptive use that characterize the baby boom generation would be expected to put women born between 1950 and 1965 at higher risk. However, birth-cohort data indicate that breast cancer mortality is not elevated in these women; in contrast, mortality for U.S. white women born in the 1930s and 1940s has unexpectedly decreased [Tarone et al., 1997]. Both white and African American baby boomers were at lower risk than previous generations were [Chu et al., 1999]. Continuation of these patterns, that is, if mortality remains low for these women as they reach older ages, would suggest that an unidentified protective factor might negate the increased mortality that would be expected to accompany these sociodemographic patterns.

SURVIVAL

Five-year relative survival rates improved from 75% during the mid-1970s to 86% during the early 1990s among white women, and from 63% to 71% for African American women in the same time period; both increases contributed to the observed incidence and mortality patterns [Ries et al., 2000]. Between 1980 and 1993, 3-year survival rates increased by 0.7% annually for both U.S. whites and African Americans [Chu et al., 1999]. Based on more than 120,000 cases diagnosed between 1989 and 1996, more than 60% of breast cancers among white women were diagnosed at a localized stage and about 30% were diagnosed at a regional stage [Ries et al., 2000]. National data on survival rates among breast cancer patients are not available, but it is unlikely that geographic variations in survival greatly influence the mortality patterns [Ries et al., 2000]. Although mammographic screening has produced a "stage shift" toward increasing diagnosis at localized stages, the stage distribution among African American women was not as favorable: localized stages accounted for one-half and regional stages accounted for one-third of cases. Survival rates varied markedly by stage at diagnosis, from 89% or more in women with localized disease to 22% or less in women whose tumors have distant spread. The more favorable prognosis among whites than among African Americans persisted for patients within each stage category, perhaps because of differences in extent of disease within stage category or effectiveness of treatment.

SUMMARY AND CONCLUSION

International and intranational breast cancer incidence and mortality data tell a number of stories about the worldwide burden of this multifactorial disease. First, incidence rate differences between countries highlight the importance of inherent genetic risk in breast cancer etiology, although the rate changes among migrants, who rather quickly acquire the rates in their host country, indicate that lifestyle factors can dramatically affect risk. Identifying which lifestyle factors influence risk, and how they operate, will be critical for understanding carcinogenesis in the breast. Second, incidence rate differences within countries arise in part because of differential access to and utilization of health care resources such as screening and diagnosis. However, the data also suggest that breast cancer among young women of different racial or ethnic groups may reflect diverse disease processes. Third, changes in incidence rates over time reflect more widespread use of mammographic screening and improvements in data collection and diagnosis, but the consistent increase suggests that the true worldwide incidence is increasing. Continued efforts to identify populations in which risk is increasing and to understand the components of those increases will be needed to appropriately design and conduct analytic investigations of breast cancer risk factors. Fourth, because of the challenges in comparing incidence and mortality data, age–period–cohort analyses are useful for understanding the potentially modifiable factors that affect disease rates. Decreasing mortality trends in young women are encouraging, but decreasing trends that are limited to older white women demonstrate the critical need to extend therapeutic advances to all segments of the population.

Despite extensive historical and current investigation, only about 55% of breast cancer cases can be explained by currently identified risk factors [Bruzzi et al., 1985]. Future investigations that take clues from population-based data and utilize multidisciplinary methods should continue to increase our understanding of the factors that contribute to the recent increases in breast cancer burden worldwide. Such an approach should increase the probability of identifying suitable targets for breast cancer prevention.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Dan Grauman of the National Cancer Institute, and Joan Hertel, Stella Sentiti, and John Lahey of IMS, Inc., Silver Spring, MD, for data development and figure generation.

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